REMARKS

Claims 1-27, 33, 34 and 36-39 were pending in this application. Of these, claims 1-27 were under consideration. All the claims were rejected as obvious over two combinations of references as discussed below. A further rejection of claim 2 was made under §112, 2nd paragraph.

Claim 2 is being amended to correct the dependency (a result of a clerical error which was the sole basis of the §112 rejection) and to improve its clarity by amending "a target sequence" to "one target sequence".

Claims 33, 34, and 36-39 are now being canceled.

Therefore Claims 1-27 remain in the case. No new matter is introduced by these amendments.

Applicants' traversals of all of the art rejections appear below. Entry of the amendments and remarks are respectfully requested, as is passage of these claims to allowance.

I. Formalities (*Specification*)

The disclosure is objected to because it contains an embedded **hyperlink** and/or other form of browser-executable code. Applicant is required to delete such embedded hyperlink or browser-executable code.

Applicants' Response

The specification has been amended above to remove this hyperlink, so that the specification is now in compliance with the requirement.

II. Rejections for Lack of Enablement under 35 U.S.C. §112, 2nd Paragraph

Claims 2-8 and 16 are rejected as being **indefinite** because claim 2 depends from itself and each of the further dependent claims depend from claim 2.

Applicants' Response

The typographical error in claim 2 has been corrected so that claim 2 depends from claim 1, rendering this rejection moot.

III. Rejection Under 35 U.S.C. 103(a)

Two rejections were made, which are noted separately below but are discussed together.

First Obviousness Rejection

Claims 1-14 and 16-24 were rejected as being obvious over Schouten *et al.* (EP 1130113; September 5, 2001) (hereinafter, "**Schouten**") in view of Tang *et al.* (*Nucleic Acids Research,* 1995, *23*:3126-31) (hereinafter, "**Tang**").

Applicants note that claims 15 and 25-27 were free of this rejection.

The Office Action goes through a detailed listing of what Schouten allegedly teaches (not reiterated here for brevity) in connection with each of the rejected claims. The Action admits that Schouten **does not teach** that the tag sequence comprises a restriction site (10) for a restriction enzyme, or step (A) which restriction site (10) is located between the primer-binding site and the section of the oligonucleotide probe (4, 6) that is complementary to the first (5) or second part (7) of the target sequence. **Schouten** also **does not teach** the step (e) of digesting the amplified connected probes with the restriction enzyme to produce a detectable fragment (21).

However, the Office Action brings in Tang as allegedly making up for these deficiencies in Schouten. Tang allegedly teaches a method of mass spectroscopic analysis of DNA probes and includes a teaching of the inclusion of restriction sites for cleavage of tags (Abstract, p. 3130, col. 2). The Action goes on to apply the combination of Schouten and Tang in detail against claims 1, 8 and 14.

The Office concluded that it would have been *prima facie* obvious to have extended the teachings of **Schouten** to incorporate the restriction site into the mass spec analysis as taught by **Tang** to arrive at the claimed invention with a reasonable expectation of success. The Action quotes from **Tang** that

> … a restriction site could be positioned such that most of the known primer sequence is cut off prior to mass spectrometry. Thus actual and valuable sequence information could be obtained, even if only short Sanger ladders are produced and analyzed

(at p. 3130, col. 2, under the heading 'Potential Applications in Molecular Biology'). The Office takes that position that one of ordinary skill in the art would have been motivated to have extended the teachings of **Schouten** to incorporate the restriction site into the mass spec analysis as taught by **Tang** to arrive at the claimed invention with a reasonable expectation for success.

Second Obviousness Rejection

Claims 15 and 25-27 (those free of the prior rejection) were rejected as being obvious over **Schouten** (*supra)* in view of **Tang** (*supra*) as applied to claims 1-14 and 16-24 above and further in view of **Vos** *et al.* (*Nucleic Acids Research*, 1995, *23:*4407-44014) (hereinafter,

"Vos"). **Schouten** allegedly teaches a method comprising multiplex ligation and a detection assay (citing to the Abstract). **Schouten** in view of **Tang** allegedly teach the limitations of claims 1-24.

However, the Action admits that neither **Schouten** or **Tang** teach the inclusion of a selective primer during the amplification step. **Vos** allegedly teaches a method of selective amplification of restriction fragments (citing to the Abstract). The Action goes on to conclude that it would have been *prima-facie* obvious to one of ordinary skill in the art at the time the to have extended the method of Schouten as supplemented by **Tan**g to incorporate the selective primer of **Vos** to arrive at the claimed invention with a reasonable expectation for success.

The Office quotes from the **Vos** *abstract* that

> ...selective amplification is achieved by the use of primers that extend into the restriction fragments, amplifying only those fragments in which the primer extensions match the nucleotides flanking the restriction sites...

and

> allows the specific co-amplification of high numbers of restriction fragments...

The Office Action alleges that one of ordinary skill in the art would have been motivated (thought the reasons why are not given) to have extended the method of Schouten and Tang to incorporate the selective primer of Vos to arrive at the claimed invention with a reasonable expectation for success (for reasons not given).

Applicants' Response

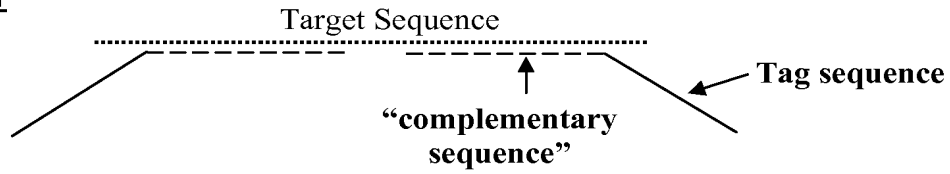
Brief Reiteration and Illustration of the Present Invention

The present claims are to a method for the multiplex detection of target sequences. In brief, the method comprises the following steps(see also Figs. 1-3 of the Application):

- an oligonucleotide ligation assay using a first and a second oligonucleotide probe for each target sequence;
- an amplification step; and
- a detection step based on molecular mass.

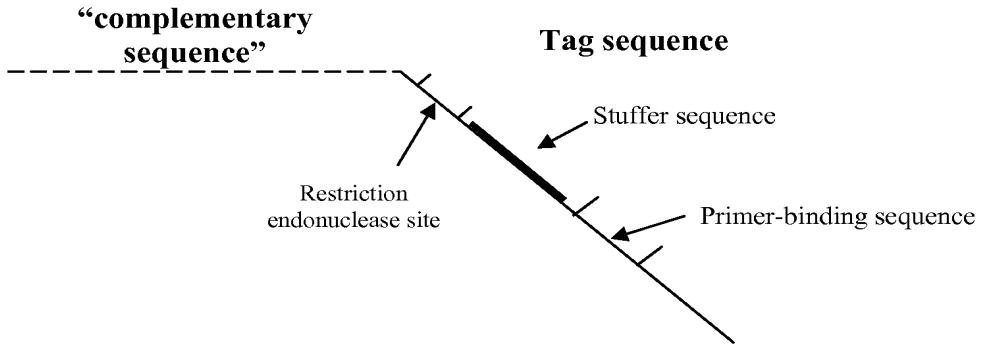
Each oligonucleotide probe comprises (a) "complementary sequence" (dashed line in Diagram 1, below), referred to in the claims as 'a section that is complementary to a first or second portion of a target sequence," and (b) a tag sequence (solid line in Diagram 1) that is not complementary to the target sequence to be detected. (The target sequence is shown as a dotted line.)

Diagram 1



The tag sequence comprises a primer-binding sequence, and at least one of the tag sequences comprises a stuffer sequence and an restriction endonuclease (recognition) site - represented in Diagram 2, below). The restriction site is located between the stuffer sequence and the first (or second) portion of the complementary sequence. This is illustrated in Diagram 2, which is an enlargement of part of Diagram 1 that shows the "parts" of the **Tag sequence** of an oligonucleotide probe as employed in the present invention. The Tag sequence also comprises a stuffer sequence and a restriction endonuclease recognition site.

Diagram 2



After amplification, the amplicons are digested with a restriction endonuclease to provide a **small detectable fragment** comprising the stuffer sequence. (See also, Diagram 4, below, which shows a comparison to the prior art methods.) This small detectable fragment does not include the "complementary sequence" (*i.e.*, the section that is complementary to a first portion of the target sequence). The stuffer sequence imparts a unique mass to each detectable fragment in the sample. The unique mass of the detectable fragment provided by the stuffer sequence allows for the identification of the target sequence in the sample.

The Schouten Technology

Indeed, as pointed out by the Office, like the present invention, Schouten too deals with multiplex ligation amplification assays. Schouten discloses a multiplex ligation-dependent amplification assay comprising:

- an oligonucleotide ligation assay (OLA) step;
- amplification;
- detection of amplicons via a detection method based upon molecular mass, *e.g.*, mass spectrometry (MS).

According to Schouten, the oligonucleotide probes employed in the OLA comprise **tag sequences** which also include **primer-binding sequences**. Schouten also discloses that **size differences** may be generated by the introduction of **stuffers**. However, importantly, the probe of Schouten **differs from the present probe** in that the tag sequence does **NOT** comprise a restriction endonuclease site located between the stuffer sequence and the *complementary sequence* (the "sequence section that is complementary to a portion of the target sequence"0.

The significant step forward, and the technical effect, of this difference is that MS now becomes a feasible and reliable technique for determining the presence (or absence) of a **target sequence** in a nucleic acid sample. This is because once amplicons are formed (indicative of the presence of a target sequence), these can be determined rapidly by MS of a very small fragment comprising the **primer-binding sequence** and the **stuffer sequence**, but **excluding** the "complementary sequence." (See Diagram 3 below, explained in more detail in the remarks that follow.)

Thus the presently claimed invention provides an improved method for determining the presence or absence of a target sequence in a nucleic acid sample by means of detecting molecular mass (as by mass spectrometry). The present invention's novel and unobvious contribution is based in part on the incorporation of a **restriction endonuclease site** in one of the oligonucleotide probes used for OLA in a location between the stuffer sequence and the "complementary sequence." After restriction by the restriction endonuclease, all that one has to do is to determine, *e.g.*, by MS, the presence of only a small fragment comprising the primer-binding sequence and the stuffer sequence of the probe. This determines the presence or absence of the target sequence in the nucleic acid sample. MS of such small oligonucleotide fragments is very fast, easy and reliable.

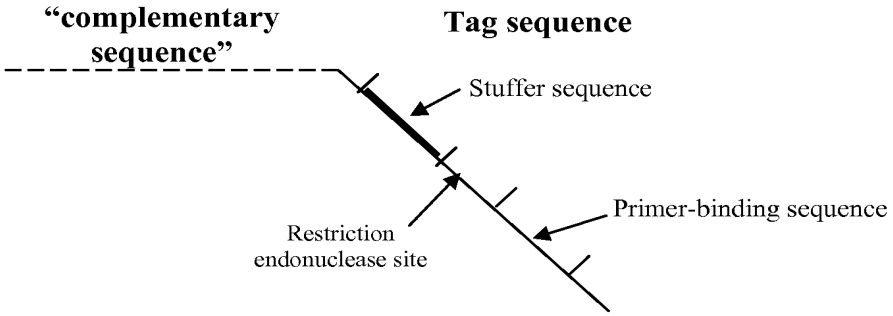
The Tang Disclosure

Tang deals with MS of duplex DNA probes. Tang discloses on page 3130, final paragraph (emphasis added) , that

> A restriction site could be positioned **such that most of the known primer sequence is cut off** prior to mass spectrometry. Thus, actual and valuable sequence information could be obtained…

Diagram 3 below shows the probe that results from modification of Schouten using the teaching of Tang (*"positioning such that most of the known primer sequence is cut off…"*): This is the probe upon which the obviousness rejection is based.

Diagram 3



Here, because of the location of the restriction site, The fragment comprising the **stuffer sequence** and the ***"complementary sequence"*** would be subjected to MS to obtain the desired information. (See also Diagram 4, below).

However, Tang neither teaches nor suggests:

(1) the concept of locating the restriction endonuclease site between the **stuffer sequence** and the ***"complementary sequence,"*** nor

(2) the concept of using a small fragment from which the *"complementary sequence"* has been digested away to determine the presence/absence of a target sequence in the nucleic acid sample being examined.

So even if there were a reasonable basis (either a teaching or even a suggestion) in either Schouten or Tang (or, more generally, in the relevant art) to combine Schouten with Tang, which Applicants contend there is not, it would not lead to the present invention. Rather, the only way that these references could have can been connected in the way the Office has done to reach a conclusion that the present claims are obvious is by using impermissible hindsight reconstruction based on Applicants' disclosure. Without Applicants' disclosure, there would be no motivation to combine these references.

A proper *prima facie* obviousness determination under *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988) (and *In re Dow Chemical Co.,* 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)) requires the Office to consider

> (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process" and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success ....Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

Applicants contend that the Office has not met this burden, particularly in view of what the prior art references (alone or combined) actually teach or suggest.

The Federal Circuit, in *Alza Corp. v. Mylan Laboratories, Inc.*, 80 USPQ2d, 1001 (Fed. Cir. 2006), devoted significant attention to this issue and cited extensively from it's decision opinion in *In re Kahn*, 441 F.3d 977, 985, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006). Applicants note that *Kahn* was cited with approval in the Supreme Court's opinion in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385, 1397 (2007). The *Alza* court stated:

> As we explained in *Kahn*, The motivation-suggestion-teaching test picks up where the analogous art test leaves off and informs the *Graham* analysis. To reach a **non-hindsight** driven conclusion as to whether a person having ordinary skill in the art at the time of the invention would have viewed the subject matter as a whole to have been obvious in view of multiple references, the Board must provide some **rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.** The requirement of such an explanation is consistent with governing obviousness law . . . .
>
> 441 F.3d at 987 (emphasis added).

The *Alza* court noted at 1004, that

> At its core, our anti-hindsight jurisprudence is a test that rests on the unremarkable premise that legal determinations of obviousness, as with such determinations generally, should be based on evidence rather than on mere speculation or conjecture. Our court's analysis in *Kahn* bears repeating:
>
> * * *
>
> ...[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be **some articulated reasoning with some rational underpinning** to support the legal conclusion of obviousness. This requirement is as much rooted in the Administrative Procedure Act [for our review of Board determinations], which ensures due process and non-arbitrary decision-making, as it is in § 103.
>
> *Kahn,* 441 F.3d at 987-88 (quoting *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000)) (citations omitted) (emphases added).

Again, it respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced because the cited art does not suggest the present methods (based on careful

analysis of the underlying nucleotide probe compositions and corresponding method steps) and lacks a proper basis for a motivation to combine Schouten with Tang. Applying the test for obviousness, the cited prior art does not suggest to those of ordinary skill that they carryout the claimed method nor do they reveal that the claimed invention could have been practiced with a reasonable expectation of success. Absent a hindsight analysis derived from Applicants' disclosure, there would be no guidance in the references or the art that would lead to the combining of these references (or combining them with Vos, as is discussed below) so as to achieve the result of the claims at issue. Rather, the Office appears to have reached a facile conclusion but not provided Applicants with "articulated reasoning with some rational underpinning" which they are due under *Kahn*.

The Rejection over Schouten In View of Tang further in view of Vos

Applicants contend that the above deficiencies in the rejection apply also to the second rejection under § 103 based on bringing in the Vos reference. First, the combination of the primary reference (Schouten) with the secondary reference (Tang) does not amount to a legally sufficient *prima facie* obviousness rejection of the indicated claims. Second, the addition of Vos does not cure this deficiency. Thus on these bases, the latter rejection must also fail.

In view of the foregoing, Applicants contend that it would be proper at this time to withdraw all the pending rejections under 35 U.S.C. § 103.

IV. Provisional Obviousness-Type Double Patenting

Claims 1 and 2 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 61-63 and 66-67 of copending Application No. 10/560,968 ('986 application, herein) in view of **Schouten** (*supra*) and **Tang** (*supra*).

Applicants' Response

Applicants respectfully draw the Examiner's attention to the fact that claim 61 of the '986 application (from which the other indicated claims depend) is a dependent claim from claim 32 (the main claim). Claim 32 requires the presence of two "clamp segments" on two separate oligo probes which segments are complementary so that they hybridize to one another. See Diagram 4, below. This key element is absent from the present invention. Nothing suggests the leap from this approach to that of the present claims, even if considering Schouten and Tang. Consequently, the present claims are patentably distinct from those in the noted application. Diagram 4 below compares, schematically, the method of the '986 claims, the Schouten method, the Tang method, and the method of the present invention. (See also Fig. 4 of the '968.)

It should be evident that the present claims could not be considered obvious variants of the '986 claims given the distinctions from Schouten and Tang documents. See, also, Applicants' remarks above in connection with the § 103 rejections. Therefore, this provisional double patenting rejection should be withdrawn.

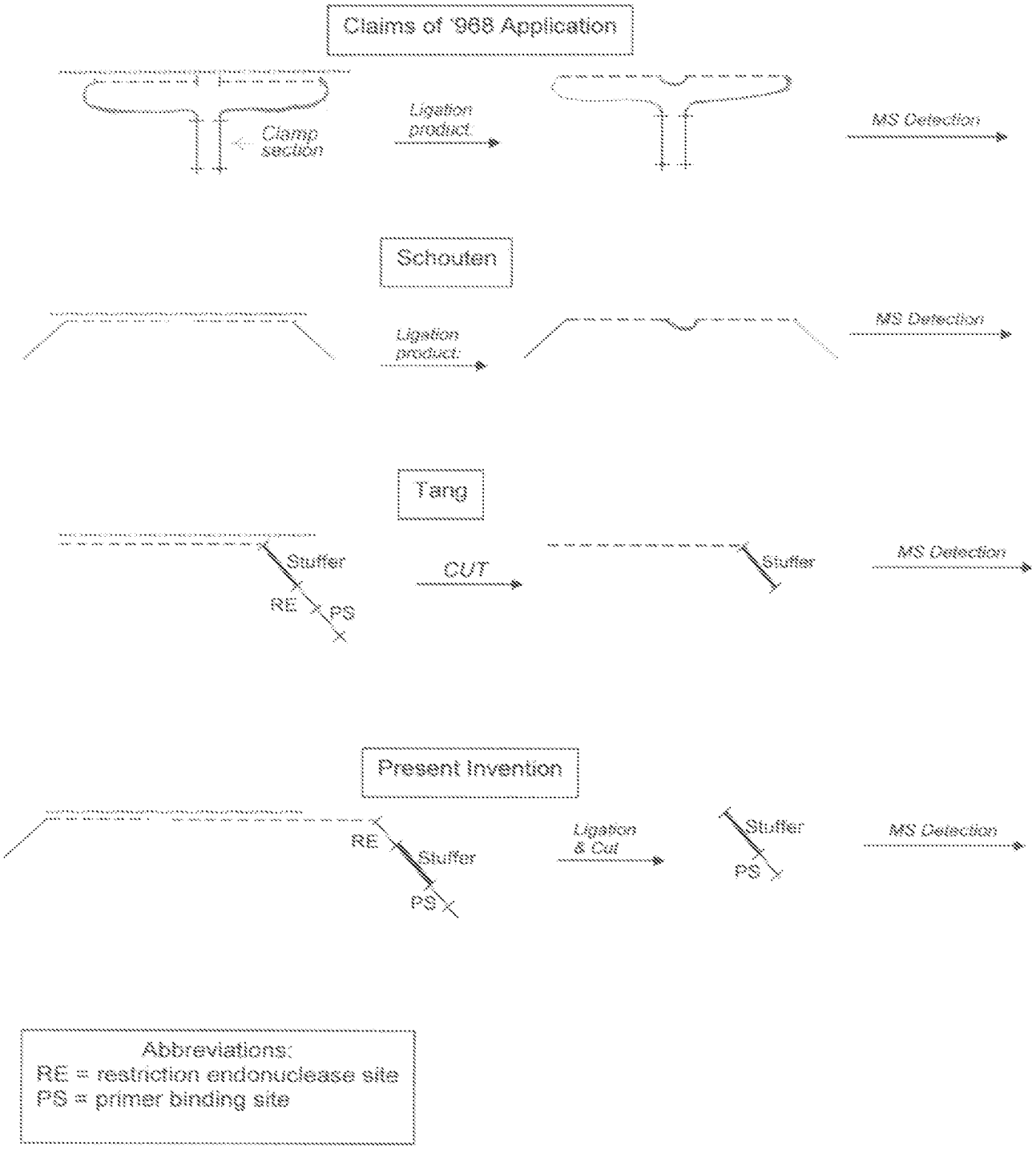


DIAGRAM 4

IV. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicants submit that the present claims are in condition for allowance, and respectfully requests early notice of such favorable action.

The Examiner is kindly requested to contact the undersigned at (202) 628-5197, if that will assist in the examination.

Respectfully submitted,

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